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FILE 'USPAT' ENTERED AT 11:42:09 ON 07 JUN 1999

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*        U. S.   P A T E N T   T E X T   F I L E             *
*                                                            *
*  THE WEEKLY PATENT TEXT AND IMAGE DATA IS CURRENT          *
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*                                                            *
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=> s (c9)(P)(complement)(P)(antibod?)(P)(treat? or therap? or antagoni? or
inhibit? or suppress? or administ?)

          6945 C9
         42926 COMPLEMENT
         35035 ANTIBOD?
        587264 TREAT?
         89788 THERAP?
         21816 ANTAGONI?
        272906 INHIBIT?
        132567 SUPPRESS?
        118345 ADMINIST?
L1         127 (C9)(P)(COMPLEMENT)(P)(ANTIBOD?)(P)(TREAT? OR THERAP? OR AN
TAG
               ONI? OR INHIBIT? OR SUPPRESS? OR ADMINIST?)

=> d l2 and cd59

'L2' NOT FOUND

=> s l1 and cd59

            41 CD59
L2           4 L1 AND CD59

=> d l2 1-4 date

                                                          L2: 1 of 4
TITLE:          C9 complement inhibitor
US PAT NO:      5,843,884                 DATE ISSUED:    Dec. 1, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/559,492                DATE FILED:     Nov. 15, 1995

                                                          L2: 2 of 4
TITLE:          Universal donor cells
US PAT NO:      5,705,732                 DATE ISSUED:    Jan. 6, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/087,007                DATE FILED:     Jul. 1, 1993
REL-US-DATA:    Continuation-in-part of Ser. No. 906,394, Jun. 29, 1992,
                  abandoned, and Ser. No. 271,562, Feb. 7, 1994, Pat. No.
                  5,573,940, which is a continuation-in-part of Ser. No.
                  729,926, Jul. 15, 1991, abandoned, which is a
                  continuation-in-part of Ser. No. 365,199, Jun. 12, 1989,
                  Pat. No. 5,135,916.

                                                          L2: 3 of 4
TITLE:          Cells expressing high levels of CD59
US PAT NO:      5,573,940                 DATE ISSUED:    Nov. 12, 1996
                [IMAGE AVAILABLE]
APPL-NO:        08/271,562                DATE FILED:     Jul. 7, 1994
REL-US-DATA:    Continuation of Ser. No. 729,926, Jul. 15, 1991,
                  abandoned, which is a continuation-in-part of Ser. No.
                  365,199, Jun. 12, 1989, Pat. No. 5,135,916.

                                                          L2: 4 of 4
TITLE:          Retroviral transduction of cells using soluble complement
                  inhibitors
US PAT NO:      5,562,904                 DATE ISSUED:    Oct. 8, 1996
                [IMAGE AVAILABLE]
APPL-NO:        08/278,550                DATE FILED:     Jul. 21, 1994

=> d l2 1-4 kwic
```

US PAT NO: 5,843,884 [IMAGE AVAILABLE] L2: 1 of 4

ABSTRACT:
Pharmaceutical . . . based on the criticality of a portion of C9 for assembly of the C5b9 complex, which specifically modulate binding of **CD59** to C9, either molecules structurally mimicking C9 amino acid residues 359 to 384 which bind to **CD59** or molecules binding to C9 amino acid residues 359 to 384. Molecules which inhibit **CD59** binding include peptides containing residues 359-384 which compete for binding with the other components of the C5b9 complex and anti-idiotypic. . .

SUMMARY:

BSUM(8)

There . . . Acad. Sci., U.S.A. 83, 6975-6979 (1986) and Schonermark, S., et al., J. Immunol. 136, 1772-1776 (1986), and the leukocyte antigen **CD59**, described by Sugita, Y., et al., J. Biochem. (Tokyo) 104, 633-637 (1988); Holguin, M. H., et al., (1989); Sims, P.. . . et al., (1990). Accumulated evidence suggest that these two proteins exhibit quite similar properties, including the following: both HRF and **CD59** are tethered to the cell surface by a glycolipid anchor, and are deleted from the membranes of the most hemolytically. . . is species-restricted, showing selectivity for C8 and C9 that are derived from homologous (i.e. human) serum; and both HRF and **CD59** appear to function by inhibiting the activation of C9 , decreasing the incorporation of C9 into the membrane C5b-9 complex,. . .

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=> d his

     (FILE 'USPAT' ENTERED AT 11:42:09 ON 07 JUN 1999)
L1           127 S (C9)(P)(COMPLEMENT)(P)(ANTIBOD?)(P)(TREAT? OR THERAP? OR
 AN
L2             4 S L1 AND CD59

=> s l1(P)(diseas?)

         90298 DISEAS?
L3           5 L1(P)(DISEAS?)

=> d l3 1-5 date

                                                          L3: 1 of 5
TITLE:          C9 complement inhibitor
US PAT NO:      5,843,884                  DATE ISSUED:   Dec. 1, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/559,492                 DATE FILED:    Nov. 15, 1995

                                                          L3: 2 of 5
TITLE:          Inhibition of complement mediated inflammatory response
US PAT NO:      5,763,156                  DATE ISSUED:   Jun. 9, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/769,382                 DATE FILED:    Dec. 19, 1996
REL-US-DATA:    Division of Ser. No. 465,548, Jun. 5, 1996, Pat. No.
                  5,660,825, which is a division of Ser. No. 243,540, May
                  16, 1994, Pat. No. 5,550,108, which is a continuation of
                  Ser. No. 813,432, Dec. 24, 1991, abandoned, which is a
                  division of Ser. No. 365,199, Jun. 12, 1989, Pat. No.
                  5,135,916.

                                                          L3: 3 of 5
TITLE:          Method of inhibition of complement mediated inflammatory
                  response
US PAT NO:      5,660,825                  DATE ISSUED:   Aug. 26, 1997
                [IMAGE AVAILABLE]
APPL-NO:        08/465,548                 DATE FILED:    Jun. 5, 1995
REL-US-DATA:    Division of Ser. No. 243,540, May 16, 1994, Pat. No.
                  5,550,108, which is a continuation of Ser. No. 813,432,
                  Dec. 24, 1991, abandoned, which is a division of Ser.
                  No. 365,199, Jun. 12, 1989, Pat. No. 5,135,916.

                                                          L3: 4 of 5
TITLE:          Cells expressing high levels of CD59
US PAT NO:      5,573,940                  DATE ISSUED:   Nov. 12, 1996
                [IMAGE AVAILABLE]
APPL-NO:        08/271,562                 DATE FILED:    Jul. 7, 1994
REL-US-DATA:    Continuation of Ser. No. 729,926, Jul. 15, 1991,
                  abandoned, which is a continuation-in-part of Ser. No.
                  365,199, Jun. 12, 1989, Pat. No. 5,135,916.

                                                          L3: 5 of 5
TITLE:          Inhibition of complement mediated inflammatory response
US PAT NO:      5,550,108                  DATE ISSUED:   Aug. 27, 1996
                [IMAGE AVAILABLE]
```

APPL-NO: 08/243,540 DATE/FILED: May 16, 1994
REL-US-DATA: Continuation of Ser. No. 813,432, Dec. 24, 1991, abandoned, which is a division of Ser. No. 365,199, Jun. 12, 1989, Pat. No. 5,135,916.

=> d l3 1-5 kwic

US PAT NO: 5,843,884 [IMAGE AVAILABLE] L3: 1 of 5

SUMMARY:

BSUM(9)

In . . . Sims and Wiedmer discelose compositions and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain CD59, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . in vitro storage. In one variation of this embodiment, the vascular endothelium of organs and tissues to be transplanted are **treated** with these compositions to protect these cells from **complement** activation after transplantation. In another embodiment, immune **disease** states are **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo. Also disclosed are methods for the production of isolated polypeptides that are able to **suppress complement** C5b-9 mediated platelet and endothelial cell activation.

US PAT NO: 5,763,156 [IMAGE AVAILABLE] L3: 2 of 5

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . secretion of proteolytic enzymes and the exposure of the procoagulant membrane receptors during collection and in vitro storage. Further, immune **disease** states can be **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

US PAT NO: 5,660,825 [IMAGE AVAILABLE] L3: 3 of 5

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the

C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . . secretion of proteolytic enzymes and the exposure of the procoagulant membrane receptors during collection and in vitro storage. Further, immune **disease** states can be **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

CLAIMS:

CLMS(1)

We claim:

1. A method for the **treatment** of autoimmune disorders and other **complement**-mediated **disease** states in a patient requiring such **treatment** comprising:

administering an effective mount of a composition containing as the active agent a C5b-9 inactivator having the ability to **inhibit** C5b-9 mediated platelet or endothelial cell activation and cytolysis selected from the group consisting of an 18 kDa C5b-9 **inhibitory** protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, wherein the molecular weights are determined by SDS-PAGE under non-reducing conditions and the inactivator proteins are of the same origin as the **complement** proteins to be **inhibited**, monoclonal **antibodies** that block membrane binding of the C5b-9, monoclonal **antibodies** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that block **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface or membrane bound molecules in **inhibiting** C5b-9 activity; and a pharmaceutically acceptable carrier.

US PAT NO: 5,573,940 [IMAGE AVAILABLE] L3: 4 of 5

SUMMARY:

BSUM(11)

In . . . Sims and Wiedmer disclose compositions and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain CD59, an 18 kDa protein found on the surface of human erythrocytes, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . in vitro storage. In one variation of this embodiment, the vascular endothelium of organs and tissues to be transplanted are **treated** with these compositions to protect these cells from **complement** activation after transplantation. In another embodiment, immune **disease** states are **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo. Also disclosed are methods for the production of isolated polypeptides that are able to **suppress complement** C5b-9 mediated platelet and endothelial cell activation.

US PAT NO: 5,550,108 [IMAGE AVAILABLE] L3: 5 of 5

ABSTRACT:

A composition and methods for use thereof relating to polypeptides having

the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . secretion of proteolytic enzymes and the exposure of the procoagulant membrane receptors during collection and in vitro storage. Further, immune **disease** states can be **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

=> d l3 1-5 fro

US PAT NO: 5,843,884 [IMAGE AVAILABLE] L3: 1 of 5
DATE ISSUED: Dec. 1, 1998
TITLE: C9 complement inhibitor
INVENTOR: Peter J. Sims, Mequon, WI
ASSIGNEE: Oklahoma Medical Research Foundation, Oklahoma City, OK (U.S. corp.)
APPL-NO: 08/559,492
DATE FILED: Nov. 15, 1995
INT-CL: [6] A01N 1/00; A61K 38/00; A61K 39/395; C07K 16/00
US-CL-ISSUED: 514/2; 530/324, 387.1, 387.2; 424/131.1, 138.1
US-CL-CURRENT: 514/2; 424/131.1, 138.1; 530/324, 387.1, 387.2
SEARCH-FLD: 424/138.1, 131.1; 536/23.1; 530/300, 350, 324, 387.1, 387.2; 514/2
REF-CITED:

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ART-UNIT: 162
PRIM-EXMR: Lila Feisee
ASST-EXMR: Susan Ungar
LEGAL-REP: Arnall Golden & Gregory, LLP

ABSTRACT:
Pharmaceutical compositions are designed based on the criticality of a portion of C9 for assembly of the C5b9 complex, which specifically modulate binding of CD59 to C9, either molecules structurally mimicking C9 amino acid residues 359 to 384 which bind to CD59 or molecules binding to C9 amino acid residues 359 to 384. Molecules which inhibit CD59 binding include peptides containing residues 359-384 which compete for binding with the other components of the C5b9 complex and anti-idiotypic antibodies immunoreactive with C9 amino acid residues 359 to 384. Molecules which prevent assembly of the C5b-9 complex include antibodies and antibody fragments immunoreactive with amino acid residues 359 to 384 of C9, peptides that bind to amino acid residues 359 to 384 of C9, and nucleotide molecules that bind to amino acid residues 359 to 384 of C9.
4 Claims, 8 Drawing Figures

US PAT NO: 5,763,156 [IMAGE AVAILABLE] L3: 2 of 5
DATE ISSUED: Jun. 9, 1998
TITLE: Inhibition of complement mediated inflammatory response
INVENTOR: Peter J. Sims, Oklahoma City, OK
Therese Wiedmer, Oklahoma City, OK
ASSIGNEE: Oklahoma Medical Research, Oklahoma City, OK (U.S. corp.)
APPL-NO: 08/769,382
DATE FILED: Dec. 19, 1996
REL-US-DATA: Division of Ser. No. 465,548, Jun. 5, 1996, Pat. No. 5,660,825, which is a division of Ser. No. 243,540, May 16, 1994, Pat. No. 5,550,108, which is a continuation of Ser. No. 813,432, Dec. 24, 1991, abandoned, which is a division of Ser. No. 365,199, Jun. 12, 1989, Pat. No. 5,135,916.
INT-CL: [6] C12Q 1/00; C12Q 1/02; G01N 33/53; G01N 33/567
US-CL-ISSUED: 435/4, 2, 7.1, 7.2, 7.21, 29, 325, 366, 372, 374; 436/821; 604/7
US-CL-CURRENT: 435/4, 2, 7.1, 7.2, 7.21, 29, 325, 366, 372, 374; 436/821; 604/7
SEARCH-FLD: 436/821; 435/2, 4, 7.1, 7.2, 7.21, 26, 325, 366, 372, 374; 604/7
REF-CITED:

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Sims et al, Biochemistry vol. 13 p. 3315, 1974.
ART-UNIT: 186
PRIM-EXMR: Sheela Huff
LEGAL-REP: Arnall Golden & Gregory, LLP

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex

activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa protein found on the surface of human platelets, a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell necrosis or stimulated secretion of proteolytic enzymes and the exposure of the procoagulant membrane receptors during collection and in vitro storage. Further, immune **disease** states can be **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

8 Claims, 9 Drawing Figures

US PAT NO: 5,660,825 [IMAGE AVAILABLE] L3: 3 of 5
DATE ISSUED: Aug. 26, 1997
TITLE: Method of inhibition of complement mediated inflammatory response
INVENTOR: Peter J. Sims, Oklahoma City, OK
Therese Wiedmer, Oklahoma City, OK
ASSIGNEE: Oklahoma Medical Research Foundation, Oklahoma City, OK (U.S. corp.)
APPL-NO: 08/465,548
DATE FILED: Jun. 5, 1995
REL-US-DATA: Division of Ser. No. 243,540, May 16, 1994, Pat. No. 5,550,108, which is a continuation of Ser. No. 813,432, Dec. 24, 1991, abandoned, which is a division of Ser. No. 365,199, Jun. 12, 1989, Pat. No. 5,135,916.
INT-CL: [6] A61K 39/395; A61K 38/00; C07K 16/00
US-CL-ISSUED: 424/130.1, 131.1, 141.1, 158.1, 810; 514/2, 12; 530/387.2, 388.25
US-CL-CURRENT: 424/130.1, 131.1, 141.1, 158.1, 810; 514/2, 12; 530/387.2, 388.25
SEARCH-FLD: 424/131.1, 130.1, 141.1, 158.1, 810; 514/12, 2; 530/387.2, 388.25
REF-CITED:

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Yamashina et al New England Journal of Medicine vol. 323 p. 1184 Oct. 1990.
Rother et al Blood vol. 84 p. 2604--abstract only 1994.

ART-UNIT: 186
PRIM-EXMR: Toni R. Scheiner
ASST-EXMR: Sheela J. Huff
LEGAL-REP: Arnall Golden & Gregory

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa protein found on the surface of human platelets, a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell necrosis or stimulated secretion of proteolytic enzymes and the exposure of the procoagulant membrane receptors during collection and in vitro storage. Further,

immune **disease** states can be **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

10 Claims, 9 Drawing Figures

US PAT NO: 5,573,940 [IMAGE AVAILABLE] L3: 4 of 5
DATE ISSUED: Nov. 12, 1996
TITLE: Cells expressing high levels of CD59
INVENTOR: Peter J. Sims, Mequon, WI
Alfred L. M. Bothwell, Guilford, CT
ASSIGNEE: Oklahoma Medical Research Foundation, Oklahoma City, OK (U.S. corp.)
Yale University, New Haven, CT (U.S. corp.)
APPL-NO: 08/271,562
DATE FILED: Jul. 7, 1994
REL-US-DATA: Continuation of Ser. No. 729,926, Jul. 15, 1991, abandoned, which is a continuation-in-part of Ser. No. 365,199, Jun. 12, 1989, Pat. No. 5,135,916.
INT-CL: [6] C12N 5/10
US-CL-ISSUED: 435/240.2, 69.1; 424/93.21
US-CL-CURRENT: 435/362; 424/93.21; 435/69.1
SEARCH-FLD: 435/240.2, 69.1; 424/93.21
REF-CITED:

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4,916,219	4/1990	Linhardt et al.	536/21
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ART-UNIT: 182
PRIM-EXMR: Stephen G. Walsh
LEGAL-REP: Arnall Golden & Gregory

ABSTRACT:
A method and means for protecting cells and transplanted organs for the effects of activated complement proteins generated in blood serum or plasma by introducing the gene for CD59 into the cells to be protected is described. In an example of the method, protection against the pore-forming activity of the human C5b-9 proteins was conferred on CHO cells by transfection with cDNA encoding the human complement regulatory protein CD59.

6 Claims, 6 Drawing Figures

US PAT NO: 5,550,108 [IMAGE AVAILABLE] L3: 5 of 5
DATE ISSUED: Aug. 27, 1996
TITLE: Inhibition of complement mediated inflammatory response
INVENTOR: Peter J. Sims, Oklahoma City, OK
Therese Wiedmer, Oklahoma City, OK
ASSIGNEE: Oklahoma Medical Research Foundation, Oklahoma City, OK (U.S. corp.)
APPL-NO: 08/243,540
DATE FILED: May 16, 1994
REL-US-DATA: Continuation of Ser. No. 813,432, Dec. 24, 1991, abandoned, which is a division of Ser. No. 365,199, Jun. 12, 1989, Pat. No. 5,135,916.
INT-CL: [6] C07K 15/00; A61K 37/02; A61K 37/64
US-CL-ISSUED: 514/21, 2, 8, 12; 530/350, 380, 830
US-CL-CURRENT: 514/21, 2, 8, 12; 530/350, 380, 830
SEARCH-FLD: 514/2, 8, 12, 21
REF-CITED:

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4,695,460	9/1989	Holme	424/101
4,916,219	4/1990	Linhandt et al.	536/21

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Rollins and Sims "The complement-inhibitory activity of CD59 resides in its capacity to block incorporation of C9 into membrane C5b-9", submitted to J. immunol. (1989).

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Hamilton, et al., "Complement Proteins C5b-9 Increase Endothelial Prothrombinase Activity" Circulation (1989).

Hamilton, et al., "Complement Proteins C5b-9 Induce vesiculation of the Endothelial Plasma Membrane and Expose Catalytic Surface for Assembly of the Prothrombinase Enzyme Complex", submitted to J. Biol. Chem.

Wiedmer, et al., "The Role of Calcium and Calpain in Complement-Induced Vesiculation of the Platelet Plasma Membrane and in the Exposure of the Platelet Factor Va Receptor".

Pandburn, et al. Proc. Natl. Acad. Sci. USA 80, 5430 (1983).

Shin, et al., J. Immunol. 136(5), 1777-1782 (1986).

Zalman, et al., Proc. Natl. Acad. Sci. USA 83, 6975 (1986).

Schonermark, et al., J. Immunol. 136, 1772 (1986).

Martin, et al., Proc. Natl. Acad. Sci. USA 85, 213-217 (1988).

Sugita, et al., J. Biochem. (Japan), 104, 633-637.

Okada, et al., Biochem. Biophys. Res. Comm. 162, 1553 (Aug. 1989).

Davies, et al., J. Exp. Med. 170, 637 (Sep. 1989).
Rollins, et al., Complement and Inflammation 6, 394 (1989).
Wiedmer and Sims, J. Biol. Chem. 260 8014-8019 (1985).
Wiedmar, et al., J. Biol. Chem. 262, 13674-13681 (1987).
Sims, et al., J. Biol. Chem. 263, 18205-18212 (1988).
Abstracts presented at XIII International Complement Workshop in San Diego, Sep. 10-15 (1989).
ART-UNIT: 184
PRIM-EXMR: Robert A. Wax
ASST-EXMR: William W. Moore
LEGAL-REP: Arnall Golden & Gregory

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell necrosis or stimulated secretion of proteolytic enzymes and the exposure of the procoagulant membrane receptors during collection and in vitro storage. Further, immune **disease** states can be **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.
5 Claims, 9 Drawing Figures

=> d l1 1-127

=> d l1 1-10,25,26,79,80,104,111,119 kwic

US PAT NO: 5,843,884 [IMAGE AVAILABLE] , L1: 1 of 127

SUMMARY:

BSUM(9)

In . . . Sims and Wiedmer disclose compositions and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain CD59, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . in vitro storage. In one variation of this embodiment, the vascular endothelium of organs and tissues to be transplanted are **treated** with these compositions to protect these cells from **complement** activation after transplantation. In another embodiment, immune disease states are **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo. Also disclosed are methods for the production of isolated polypeptides that are able to **suppress complement** C5b-9 mediated platelet and endothelial cell activation.

DETDESC:

DETD(3)

Peptide sequence in human **complement** protein **C9** has been identified that contributes to the recognition of this protein by its naturally occurring **inhibitor**, CD59 . CD59 is known to bind to neo-epitopes that become exposed in **complement** C8 and **C9** during assembly of the cytolytic membrane attack complex of proteins C5b through **C9**. Through this interaction, CD59 interrupts assembly of the C5b-9 complex, protecting the target cell from destruction by these **complement** proteins. Data demonstrates that **antibody** raised against this human **C9**-derived peptide sequence is functionally **inhibitory** towards the lytic activity of the human C5b-9 complex. This permits design of reagents directed specifically at human **C9** that mimic or **inhibit** the **complement-inhibitory** function of cell-surface CD59.

DETDESC:

DETD(65)

The capacity of **antibody** against hu **C9** peptide 359-384 to **inhibit** MAC was determined by hemolytic assay, using the chE target cells described above, omitting CD59. In these experiments, 0-1 mg/ml Fab of **antibody** against hu **C9** peptide 359-384 (or, non-immune **antibody** control) was added with recombinant **C9** (hu, rb, or chimeric), and **complement**-specific lysis determined.

US PAT NO: 5,763,156 [IMAGE AVAILABLE] L1: 2 of 127

ABSTRACT:

A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . and the exposure of the procoagulant membrane receptors during collection and in vitro storage. Further, immune disease states can be **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

SUMMARY:

BSUM(16)

A method of monitoring the effectiveness of C5b-9 **inhibition** and subsequent platelet activation comprising exposing the platelets to be transfused to a membrane potentiometric fluorescent dye and comparing the. . . Also disclosed are A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein, isolated from human erythrocyte. . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of a-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent **C9** neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis of platelets **treated** with C5b-9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(4)

As used herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of **therapeutic** efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in **inhibiting** C5b-9 activity, especially the Fab fragments of monoclonal **antibodies** having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C5b-9.

DETDESC:

DETD(64)

Taken together, these data suggest that epitopes recognized by .alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** by membrane bound C5b-8. Similar results have been obtained in studies with erythrocytes and endothelial cells. The requirement for activated **C9** (incorporated into membrane C5b-9 complexes) in the platelet responses observed in the presence of this **antibody** is underscored by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

CLAIMS:

CLMS(2)

2. The method of claim 1 wherein the platelets to be transfused have been **treated** prior to transfusion with a C5b-9 inactivator having the ability to **inhibit** C5b-9 mediated platelet or endothelial cell C5b-9 activation and cytolysis selected from the group consisting of an 18 kDa C5b-9 **inhibitory** protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity; monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that block **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface or membrane bound molecules in **inhibiting** C5b-9 activity, wherein the molecular weights are determined by SDS-PAGE under non-reducing conditions, and the **inhibitor** proteins are of the same origin as the **complement** proteins to be **inhibited**.

US PAT NO: 5,705,732 [IMAGE AVAILABLE] L1: 3 of 127

DETDESC:

DETD(28)

Sequential . . . [redacted]n-lytic alteration of specific [redacted]ell functions affecting vascular h[redacted]stases. In the case of human [redacted]thelial cells exposed to human serum **complement**, membrane deposition of the C5b-9 complex initiates a variety of procoagulant and prothrombotic changes in the cell that are expected to accelerate blood clotting and thrombus formation, as described, for example, by Hattori, et al., 1989 "**Complement** proteins C5b-9 induce secretion of high molecular weight multimers of endothelial von Willebrand Factor and translocation of granule membrane protein GMP-140 to the cell surface" J. Biol. Chem. 264:9053-9060; Hamilton, et al., 1990 "Regulatory control of the terminal **complement** proteins at the surface of human endothelial cells: Neutralization of a C5b-9 **inhibitor** by **antibody** to CD59" Blood 76:2572-2577; and Hamilton and Sims 1991 "The terminal **complement** proteins C5b-9 augment binding of high density lipoprotein and its apoproteins A-I and A-II to human endothelial cells" J. Clin. Invest. 88:1833-1840. These responses appear to depend upon insertion of **C9** into the plasma membrane of the target cell and therefore can be prevented by interfering with assembly of the C5b-9. . .

US PAT NO: 5,679,345 [IMAGE AVAILABLE] L1: 4 of 127

ABSTRACT:
Interference with formation of the **complement**-based membrane attack complex (MAC) will mitigate or even prevent tissue injury associated with the effects of **complement** in inflammation and graft rejection. Passive **treatment** of xenograft recipients at the time of and after transplantation with **antibody** against C-6, which interrupts the sequence of binding steps that form MAC, has been observed to **suppress** hyperacute xenograft rejection with no adverse signs or symptoms in the xenograft recipient. The present invention provides a method for interfering with MAC formation in transplant recipients, by **administering** compounds which interrupt one or more of the binding reactions between C5b and C6-**C9**, so that the MAC cannot form.

SUMMARY:

BSUM(30)

The present invention provides a method for **suppressing** **complement**-dependent rejection of organ transplants comprising **administering** an **inhibitor** of membrane attack complex formation (MAC formation **inhibitor**) to an organ transplant recipient in an amount effective to **suppress** cell lysis initiated by formation of the C5b-**C9** membrane attack complex. The MAC formation **inhibitor** may be a non-functional C6 analog, a non-functional C7 analog, art anti-C6 **antibody**, an anti-C7 **antibody**, or the bacterial protein TraT, which **inhibits** **complement**-dependent cell lysis at the level of C6. In a particular embodiment, the method of this invention may be used to mitigate damage to an organ graft resulting from alternative pathway activation of **complement** in a graft recipient's serum by ischemically damaged tissue in the graft organ.

SUMMARY:

BSUM(34)

Passive **treatment** of recipients with **antibody** against C-6, which interrupts the sequence of binding steps that form MAC, at the time of and after transplantation resulted. . . prevention of hyperacute xenograft rejection with no adverse signs or symptoms to the recipient. Thus, interference with formation of the **complement**-based MAC will mitigate or even prevent tissue injury associated with the effects of **complement** in inflammation and graft rejection. The present invention provides a method for such interference, by **administering** compounds

which interrupt one or more of the binding reactions between C5b and C6-**C9**, so that the M[redacted] cannot form. Examples of such [redacted]mpounds include monoclonal [redacted]**bodies** that bind either C6 o[redacted]. Although **antibodies** to human C6 are currently available as monoclonal or polyclonal **antibodies**, no attempt to utilize such **antibodies** in preventing or **treating** rejection of allografts or xenografts has been described prior to our invention.

CLAIMS:

CLMS(1)

We claim:

1. A method of **suppressing complement**-dependent rejection of an organ transplant comprising **administering** an effective amount of an **inhibitor** of membrane attack complex formation (MAC formation **inhibitor**) to a recipient of a transplant organ wherein the **inhibitor** interferes with one or more binding steps in the sequential binding of **complement** component (C5b, C6, C7, C8, and **C9**, wherein the **inhibitor** is selected from the group consisting of a non-functional C6 analog, a non-functional C7 analog, an anti-C6 **antibody** and an anti-C7 **antibody**.

CLAIMS:

CLMS(15)

15. A method of **suppressing complement**-dependent rejection of organ transplants comprising infusing an isolated organ prior to transplant of said organ into an organ transplant recipient with an anti-C6 **antibody** or an anti-C7 **antibody** in an amount effective to **suppress** cell lysis initiated by formation of the C5b-**C9** membrane attack complex.

US PAT NO: 5,660,825 [IMAGE AVAILABLE] L1: 5 of 127

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . and the exposure of the procoagulant membrane receptors during collection and in vitro storage. Further, immune disease states can be **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

SUMMARY:

BSUM(16)

A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or

antibodies against C7 or **C9** which block the formation of the C5b-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein, isolated from human erythrocyte. . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of .alpha.-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent C9neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis of platelets **treated** with C5b-9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(4)

As used herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of **therapeutic** efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in **inhibiting** C5b-9 activity, especially the Fab fragments of monoclonal **antibodies** having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C5b-9.

DETDESC:

DETD(64)

Taken together, these data suggest that epitopes recognized by .alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** by membrane bound C5b-8. Similar results have been obtained in studies with

erythrocytes and endothelial cells. The requirement for activated **C9** (incorporated into m[redacted]rane C5b-9 complexes) in the p[redacted]elet responses observed in the pres[redacted]e of this **antibody** is undersc[redacted] by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

CLAIMS:

CLMS(1)

We claim:

1. A method for the **treatment** of autoimmune disorders and other **complement**-mediated disease states in a patient requiring such **treatment** comprising:

administering an effective mount of a composition containing as the active agent a C5b-9 inactivator having the ability to **inhibit** C5b-9 mediated platelet or endothelial cell activation and cytolysis selected from the group consisting of an 18 kDa C5b-9 **inhibitory** protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, wherein the molecular weights are determined by SDS-PAGE under non-reducing conditions and the inactivator proteins are of the same origin as the **complement** proteins to be **inhibited**, monoclonal **antibodies** that block membrane binding of the C5b-9, monoclonal **antibodies** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that block **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface or membrane bound molecules in **inhibiting** C5b-9 activity; and

a pharmaceutically acceptable carrier.

US PAT NO: 5,635,178 [IMAGE AVAILABLE] L1: 6 of 127

SUMMARY:

BSUM(16)

A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein, isolated from human erythrocyte. . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of .alpha.-P18

increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-depende[redacted]**C9** neo-epitope. Although .alph[redacted]P18 causes little increase in t[redacted]cytolysis of platelets **treate**[redacted]th C5b-9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GPIIb-IIIa, release of membrane microparticles from. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(4)

As used herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of **therapeutic** efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in **inhibiting** C5b-9 activity, especially the Fab fragments of monoclonal **antibodies** having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C5b-9.

DETDESC:

DETD(64)

Taken together, these data suggest that epitopes recognized by .alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** by membrane bound C5b-8. Similar results have been obtained in studies with erythrocytes and endothelial cells. The requirement for activated **C9** (incorporated into membrane C5b-9 complexes) in the platelet responses observed in the presence of this **antibody** is underscored by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

US PAT NO: 5,573,940 [IMAGE AVAILABLE] L1: 7 of 127

SUMMARY:

BSUM(11)

In . . . Sims and Wiedmer disclose compositions and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain CD59, an 18 kDa protein found on the surface of human erythrocytes, active derivatives or fragments thereof which act to

inhibit the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . . in vitro storage. In one variation of this embodiment, the vascular endothelium of organs and tissues to be transplanted are **treated** with these compositions to protect these cells from **complement** activation after transplantation. In another embodiment, immune disease states are **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo. Also disclosed are methods for the production of isolated polypeptides that are able to **suppress complement** C5b-9 mediated platelet and endothelial cell activation.

SUMMARY:

BSUM(18)

This . . . the amplified gene expression in CD59-transfected CHO (Chinese Hamster Ovary) cells, which conferred protection on the cells from attack by **complement**. CD59 was stably expressed in Chinese hamster ovary cells using the pFRSV mammalian expression vector. After cloning and selection, the. . . the sensitivity of the CD59 transfectants to the pore-forming activity of human C5b-9. Induction of cell-surface expression of CD59 antigen **inhibited** C5b-9 pore formation in a dose-dependent fashion. CD59 transfectants expressing greater than or equal to 1.3.times.10.sup.6 molecules of CD59/cell were completely resistant to human serum **complement**. By contrast, CD59 transfectants remained sensitive to the pore-forming activity of guinea pig C8 and **C9** (bound to human C5b-67). Functionally blocking **antibody** against erythrocyte CD59 abolished the human **complement** resistance observed for the CD59-transfected Chinese hamster ovary cells. These results confirm that the C5b-9 **inhibitory** function of the human erythrocyte membrane is provided by CD59 and that the gene for this protein can be expressed in xenotypic cells to confer protection against human serum **complement**.

DETDESC:

DETD(8)

As . . . filed Jun. 12, 1989, now U.S. Pat. No. 5,135,916 the conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response were based on the following. Addition of purified CD59, isolated from human erythrocyte membranes, to other blood cells or endothelium served to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of CD59, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which includes CD59. When bound to the platelet surface, the Fab of .alpha.-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent **C9** neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis of platelets **treated** with C5b-9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with

.alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** p tiate the stimulatory respons of platelets exposed to other ago s.

DETDESC:

DETD(60)

To demonstrate **complement inhibitory** activity, CD59 expression of transfected CHO cells was amplified by growth in 50 .mu.g/ml methotrexate: the cells were loaded with. . . FIG. 3. After washing, the cells were incubated (4.degree. C., 30 min) with either 0 mg/ml or 0.5 mg/ml functionally **inhibitory antibody** (Fab fragments) to CD59. Unbound **antibody** was removed; C8 (1 .mu.g/ml) and varying amounts of **C9**) were added; and dye release was measured after 15 min at 37.degree. C.

DETDESC:

DETD(61)

As shown in FIG. 4, the resistance to **complement**-mediated membrane damage observed for CD59-expressing CHO cells reflected **inhibition** of **C9**-dependent activation of the **complement** pore, and this **inhibition** was reversed by prior incubation of the cells with Fab fragments of a functionally blocking **antibody** directed against CD59 antigen. These data confirm that the protection against human serum **complement** observed for CD59 transfectants is related to the expression of cell-surface CD59 and is not due to other changes in. . .

US PAT NO: 5,562,904 [IMAGE AVAILABLE] L1: 8 of 127

DRAWING DESC:

DRWD(4)

FIG. 2b Monoclonal **antibodies** and CoVF protect RVVPs from **complement**-mediated inactivation. Monoclonal **antibodies** specific for the human terminal **complement** components C5, C6, C7, C8, **C9** and cobra venom factor (CoVF) were assayed for the ability to protect RVVPs from human serum **complement**. Human serum (Hu Ser) was preincubated with functionally blocking mAbs against C5, C6, C7, C8, and **C9** and cobra venom factor. LXSN RVVPs preincubated in heat inactivated serum (HI Hu Ser), untreated serum (Hu Ser), serum **treated** with a nonblocking (NBL) anti-C8 mAb or LXSN RVVPs in the absence of serum were included as positive and negative. . . After pretreatment with serum, the RVVPs were titered on NIH/3T3 cells. Bars indicate the percentage of transducing RVVPs remaining following **treatment** with serum under the various conditions relative to untreated RVVPs. Data represent a single experiment, one of two so performed.

US PAT NO: 5,550,108 [IMAGE AVAILABLE] L1: 9 of 127

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . .

and the exposure of the procoagulant membrane receptors during collection and in vitro storage. Further, immune disease states be **treated** by **administering** an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

SUMMARY:

BSUM(16)

A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein, isolated from human erythrocyte. . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of .alpha.-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent **C9** neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis of platelets **treated** with C5b-9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(4)

As used herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of **therapeutic** efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9, and

anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in[redacted]**hibiting** C5b-9 activity, espec[redacted]ly the Fab fragments of monoclo[redacted] **antibodies** having this activi[redacted] All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C5b-9.

DETDESC:

DETD(64)

Taken together, these data suggest that epitopes recognized by .alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** by membrane bound C5b-8. Similar results have been obtained in studies with erythrocytes and endothelial cells. The requirement for activated **C9** (incorporated into membrane C5b-9 complexes) in the platelet responses observed in the presence of this **antibody** is underscored by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

US PAT NO: 5,135,916 [IMAGE AVAILABLE] L1: 10 of 127

SUMMARY:

BSUM(16)

A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein, isolated from human erythrocyte. . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of .alpha.-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent **C9** neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis of platelets **treated** with C5b- 9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of

these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) al[redacted] does not activate platelets, [redacted] does incubation with this **antibody** p[redacted]ntiate the stimulatory respon[redacted]of platelets exposed to other agonists.

DETDESC:

DETD(4)

As used herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of **therapeutic** efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9 , monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9 , and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in **inhibiting** C5b-9 activity, especially the Fab fragments of monoclonal **antibodies** having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C5b-9 .

DETDESC:

DETD(63)

Taken together, these data suggest that epitopes recognized by .alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** by membrane bound C5b-8. Similar results have been obtained in studies with erythrocytes and endothelial cells. The requirement for activated **C9** (incorporated into membrane C5b-9 complexes) in the platelet responses observed in the presence of this **antibody** is underscored by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

US PAT NO: 4,431,636 [IMAGE AVAILABLE] L1: 25 of 127

SUMMARY:

BSUM(7)

The **complement** system (e.g., classical pathway) can be considered to consist of three subsystems: (1) a recognition unit (C1q) which enables it to combine with **antibody** molecles that have detected a foreign invader; (2) an activation unit (C1r, C1s, C2, C4, C3) which prepares a site on the neighboring membrane; and (3) an attack unit (C5, C6, C7, C8 and **C9**) which creates a "hole" in the membrane. The membrane attack unit is non-specific; it destroys invaders only because it is. . . own cells, its activity must be limited in time. This limitation is accomplished partly by the spontaneous decay of activated **complement** and partly by interference by **inhibitors** and destructive enzymes. The control of **complement**, however, is not perfect, and there are times when damage is done to host's cells. Immunity is, therefore, a double-edged. . .

US PAT NO: 4,414,[redacted]7 [IMAGE AVAILABLE] L1: 26 of 127

SUMMARY:

BSUM(7)

The **complement** system can be considered to consist of three sub-systems: (1) a recognition unit (C1q) which enables it to combine with **antibody** molecules that have detected a foreign invader; (2) an activation unit (C1r, C1s, C2, C4, C3) which prepares a site on the neighboring membrane; and (3) an attack unit (C5, C6, C7, C8 and **C9**) which creates a "hole" in the membrane. The membrane attack unit is non-specific; it destroys invaders only because it is. . . . own cells, its activity must be limited in time. This limitation is accomplished partly by the spontaneous decay of activated **complement** and partly by interference by **inhibitors** and destructive enzymes. The control of **complement**, however, is not perfect, and there are times when damage is done to the host's cells. Immunity is, therefore, a. . .

US PAT NO: 4,147,801 [IMAGE AVAILABLE] L1: 79 of 127

SUMMARY:

BSUM(5)

The **complement** system can be considered to consist of three sub-systems: (1) a recognition unit (C1q) which enables it to combine with **antibody** molecules that have detected a foreign invader; (2) an activation unit (C1r, C1s, C2, C4, C3), which prepares a site on the neighboring membrane; and, (3) an attack unit (C5, C6, C7, C8 and **C9**) which creates a "hole" in the membrane. The membrane attack unit is non-specific; it destroys invaders only because it is. . . own cells, its activity must be limited in time. This limitation is accomplished partly by the spontaneous decay of activated **complement** and partly by interference by **inhibitors** and destructive enzymes. The control of **complement**, however, is not perfect, and there are times when damage is done to the host's cells. Immunity is therefore a. . .

US PAT NO: 4,146,640 [IMAGE AVAILABLE] L1: 80 of 127

SUMMARY:

BSUM(5)

The **complement** system can be considered to consist of three sub-systems: (1) a recognition unit (C1q) which enables it to combine with **antibody** molecules that have detected a foreign invader; (2) an activation unit (C1r, C1s, C2, C4, C3), which prepares a site on the neighboring membrane; and, (3) an attack unit (C5, C6, C7, C8 and **C9**) which creates a "hole" in the membrane. The membrane attack unit is non-specific; it destroys invaders only because it is. . . own cells, its activity must be limited in time. This limitation is accomplished partly by the spontaneous decay of activated **complement** and partly by interference by **inhibitors** and destructive enzymes. The control of **complement**, however, is not perfect, and there are times when damage is done to the host's cells. Immunity is therefore a. . .

US PAT NO: 4,103,028 [IMAGE AVAILABLE] L1: 104 of 127

SUMMARY:

BSUM(5)

The **complement** system can be considered to consist of three

sub-systems: (1) a recognition unit (C1q) which enables it to combine with **antibody** molecu[redacted] that have detected a foreign [redacted]ader; (2) an activation unit (C1r[redacted]s, C2, C4, C3), which prepar[redacted] site on the neighboring membrane; and (3) an attack unit (C5, C6, C[redacted], C8, and **C9**) which creates a "hole" in the membrane. The membrane attack unit is non-specific; it destroys invaders only because it is. . . own cells, it activity must be limited in time. This limitation is accomplished partly by the spontaneous decay of activated **complement** and partly by interference by **inhibitors** and destructive enzymes. The control of **complement**, however, is not perfect, and there are times when damage is done to the host's cells. Immunity is therefore a. . .

US PAT NO: 4,087,548 [IMAGE AVAILABLE] L1: 111 of 127

SUMMARY:

BSUM(5)

The **complement** system can be considered to consist of three sub-systems: (1) a recognition unit (C1q) which enables it to combine with **antibody** molecules that have detected a foreign invader; (2) an activation unit (C1r, C1s, C2, C4, C3), which prepares a site on the neighboring membrane; and, (3) an attack unit (C5, C6, C7, C8 and **C9**) which creates a "hole" in the membrane. The membrane attack unit is non-specific; it destroys invaders only because it is. . . own cells, its activity must be limited in time. This limitation is accomplished partly by the spontaneous decay of activated **complement** and partly be interference by **inhibitors** and destructive enzymes. The control of **complement**, however, is not perfect, and there are times when damage is done to the host's cells. Immunity is therefore a. . .

US PAT NO: 4,021,545 [IMAGE AVAILABLE] L1: 119 of 127

SUMMARY:

BSUM(8)

The **complement** system can be considered to consist of three subsystems, (1) a recognition unit (C1q) which enables it to combine with **antibody** molecules that have detected a foreign invader; (2) an activation unit, (C1r, C1s, C2, C4, C3); which prepares a site on the neighboring membrane; and (3) an attack unit (C6, C7, C8, **C9**) which creates a "hole" in the membrane. The membrane attack unit is nonspecific; it destroys invaders only because it is. . . own cells, its activity must be limited in time. This limitation is accomplished partly by the spontaneous decay of activated **complement** and partly by interference by **inhibitors** and destructive enzymes. The control of **complement**, however, is not perfect, and there are times when damage is done to the host's cells. Immunity is therefore a. . .

US PAT NO: 5,562,904 [IMAGE AVAILABLE] L2: 4 of 4

SUMMARY:

BSUM(55)

An inhibitor referred to as **CD59** (also known as "MACIF," "protectin," or "p18"), acts to block the final step in the complement cascade leading to the assemblage of the lyric C5b-9 MAC. The complement inhibitory action of **CD59** is greatest when the **CD59** molecule is attached to the surface of a cell membranes but complement inhibitory activity of soluble forms of **CD59** has also been reported. See Rooney and Morgan, 1992 and Lehto and Meri, 1993. A number of viral and non-human primate complement inhibitor proteins that are similar in structure and function to **CD59** have been described (see copending U.S. patent application Ser. No. 08/105,735, filed Aug. 11, 1993, and copending PCT patent application. . .

SUMMARY:

BSUM(64)

Herpesvirus . . . a membrane glycoprotein (mCCPH) and a secreted derivative (sCCPH). The HVS-15 protein is closely related to the endogenous human CIM, **CD59**. See, for example, copending PCT patent application Ser. No. PCT/US93/00672, filed Jan. 12, 1993.

DRAWING DESC:

DRWD(4)

FIG. 2b Monoclonal **antibodies** and CoVF protect RVVPs from **complement**-mediated inactivation. Monoclonal **antibodies** specific for the human terminal **complement** components C5, C6, C7, C8, **C9** and cobra venom factor (CoVF) were assayed for the ability to protect RVVPs from human serum **complement**. Human serum (Hu Ser) was preincubated with functionally blocking mAbs against C5, C6, C7, C8, and **C9** and cobra venom factor. LXSN RVVPs preincubated in heat inactivated serum (HI Hu Ser), untreated serum (Hu Ser), serum **treated** with a nonblocking (NBL) anti-C8 mAb or LXSN RVVPs in the absence of serum were included as positive and negative. . . After pretreatment with serum, the RVVPs were titered on NIH/3T3 cells. Bars indicate the percentage of transducing RVVPs remaining following **treatment** with serum under the various conditions relative to untreated RVVPs. Data represent a single experiment, one of two so performed.

DETDESC:

DETD(7)

Among . . . metabolic defect are also suitable for transfer into the cells of a patient. Such genes include the transmembrane form of **CD59** discussed in copending U.S. patent application Ser. No. 08/205,720, filed Mar. 3, 1994, entitled "Terminal Complement Inhibitor Fusion Genes and. . .

3/3/7
DIALOG(R)File 357:Derwent Biotechnology Abs
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0024685 DBA Accession No.: 84-07960
Construction of a new family of high efficiency bacterial expression vectors: identification of cDNA clones coding for human liver proteins - expression of foreign DNA as hybrid beta-galactosidase protein
AUTHOR: Stanley K K; Luzio J P
CORPORATE SOURCE: European Molecular Biology Laboratory, Meyerhofstrasse 1, Postfach 10.2209, D-6900, Heidelberg, Germany.
JOURNAL: EMBO J. (3, 6, 1429-34) 1984
CODEN: 3770W
LANGUAGE: English

3/3/8
DIALOG(R)File 357:Derwent Biotechnology Abs
(c) 1999 Derwent Publ Ltd. All rts. reserv.

0019524 DBA Accession No.: 84-02799
Neoantigen of the polymerized ninth component of **complement**: characterization of a monoclonal antibody and immunohistochemical localization in renal disease - hybridoma construction
AUTHOR: Falk R J; Dalmasso A P; Kim Y; Tsai C H; Scheinman J I; Gewurz H
CORPORATE SOURCE: Department of Pediatrics, University of Minnesota Medical School, Veterans Administration Medical Center, Minneapolis, Minnesota 55455, U.S.A.
JOURNAL: J.Clin.Invest. (72, 2, 560-73) 1983
CODEN: JCINAO
LANGUAGE: English
? begin 399

07jun99 09:48:16 User208760 Session D1250.3
$8.14 0.730 DialUnits File357
$31.05 23 Type(s) in Format 3
$31.05 23 Types
$39.19 Estimated cost File357
FTSNET 0.100 Hrs.
$39.19 Estimated cost this search
$39.47 Estimated total session cost 0.859 DialUnits

File 399:CA SEARCH(R) 1967-1999/UD=13023
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*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.

Set	Items	Description
? s c9 and cd59		
	2494	C9
	408	CD59
S1	15	C9 AND CD59
? rd s1		
...completed examining records		
S2	15	RD S1 (unique items)
? t s2/7/all		

2/7/1
DIALOG(R)File 399:CA SEARCH(R)
(c) 1999 American Chemical Society. All rts. reserv.

127276945 CA: 127(20)276945k JOURNAL
Enhanced sensitivi[redacted]f P-glycoprotein-positive mu rug resistant tumor cells to complement-[redacted]iated lysis
AUTHOR(S): Bomstein, Yonit; Fishelson, Zvi
LOCATION: Sackler School Medicine, Tel Aviv University, 69978, Tel Aviv-Jaffa, Israel
JOURNAL: Eur. J. Immunol. DATE: 1997 VOLUME: 27 NUMBER: 9 PAGES: 2204-2211 CODEN: EJIMAF ISSN: 0014-2980 LANGUAGE: English PUBLISHER: Wiley-VCH
SECTION:
CA215004 Immunochemistry
CA214XXX Mammalian Pathological Biochemistry
IDENTIFIERS: multidrug resistant carcinoma complement P glycoprotein
DESCRIPTORS:
Mouth diseases...
carcinoma; enhanced sensitivity of P-glycoprotein-pos. multidrug resistant tumor cells KB-V1 to complement-mediated lysis
Proteins(specific proteins and subclasses)...
C3bp (complement C3b-binding protein); enhanced sensitivity of P-glycoprotein-pos. multidrug resistant tumor cells KB-V1 to complement-mediated lysis
Complement... Multidrug resistance...
enhanced sensitivity of P-glycoprotein-pos. multidrug resistant tumor cells KB-V1 to complement-mediated lysis
CD59(antigen)... Membrane cofactor protein... P-glycoproteins...
enhanced sensitivity of P-glycoprotein-pos. multidrug resistant tumor cells to complement-mediated lysis, expression by KB-V1 cells
Carcinoma...
mouth; enhanced sensitivity of P-glycoprotein-pos. multidrug resistant tumor cells KB-V1 to complement-mediated lysis
CAS REGISTRY NUMBERS:
82986-89-8 enhanced sensitivity of P-glycoprotein-pos. multidrug resistant tumor cells KB-V1 to complement-mediated lysis
99085-47-9P enhanced sensitivity of P-glycoprotein-pos. multidrug resistant tumor cells to complement-mediated lysis, expression by KB-V1 cells
80295-59-6 poly C9; enhanced sensitivity of P-glycoprotein-pos. multidrug resistant tumor cells KB-V1 to complement-mediated lysis

2/7/2
DIALOG(R)File 399:CA SEARCH(R)

127032845 CA: 127(3)32845m PATENT
C9 complement inhibitor
INVENTOR(AUTHOR): Sims,, Peter J.
LOCATION: USA
ASSIGNEE: Oklahoma Medical Research Foundation
PATENT: PCT International ; WO 9717987 A1 DATE: 19970522
APPLICATION: WO 96US17940 (19961108) *US 559492 (19951115)
PAGES: 51 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-038/17A; C07K-014/47B DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA215005 Immunochemistry
IDENTIFIERS: CD59 binding C9 peptide tumor therapy, complement mediated inflammation C5b C9 complex
DESCRIPTORS:
Antibodies...
anti-idiotype to C9; C9 complement inhibitor
Inflammation...
complement-mediated; C9 complement inhibitor
Peptides,biological studies...

cyclized covalently of C9; C9 complement inhibitor
Antitumor agents... Anti-inflammatory drugs... CD59(antigen)... Complement ... Protein sequence
C9 complement inhibitor
CAS REGISTRY NUMBERS:
80295-55-2 80295-59-6 190775-76-9 C9 complement inhibitor

2/7/3
DIALOG(R)File 399:CA SEARCH(R)

126073587 CA: 126(6)73587b JOURNAL
Binding of human and rat CD59 to the terminal complement complexes
AUTHOR(S): Lehto, T.; Morgan, B. P.; Meri, S.
LOCATION: Dep. Bacteriology Immunology, Univ. Helsinki, Finland
JOURNAL: Immunology DATE: 1997 VOLUME: 90 NUMBER: 1 PAGES: 121-128
CODEN: IMMUAM ISSN: 0019-2805 LANGUAGE: English PUBLISHER: Blackwell
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: CD59 binding complement C8 C9
DESCRIPTORS:
CD59(antigen)... Complement... Rat...
binding of human and rat CD59 to complement C8 and C9
CAS REGISTRY NUMBERS:
80295-58-5 80295-59-6 binding of human and rat CD59 to complement C8 and C9

2/7/4
DIALOG(R)File 399:CA SEARCH(R)

124143160 CA: 124(11)143160s JOURNAL
Role of a Disulfide-Bonded Peptide Loop within Human Complement C9 in the Species-Selectivity of Complement Inhibitor CD59
AUTHOR(S): Huesler, Thomas; Lockert, Dara H.; Sims, Peter J.
LOCATION: Blood Research Institute, Blood Center of Southeastern Wisconsin, Milwaukee, WI, 53233, USA
JOURNAL: Biochemistry DATE: 1996 VOLUME: 35 NUMBER: 10 PAGES: 3263-9
CODEN: BICHAW ISSN: 0006-2960 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement C9 disulfide bonded loop CD59
DESCRIPTORS:
Antigens,CD59... Cytolysis... Disulfide group... Molecular association... Molecular structure-biological activity relationship...
human complement C9 disulfide-bonded peptide loop in the species-selectivity of complement inhibitor CD59
CAS REGISTRY NUMBERS:
80295-59-6 human complement C9 disulfide-bonded peptide loop in the species-selectivity of complement inhibitor CD59

2/7/5
DIALOG(R)File 399:CA SEARCH(R)

123109790 CA: 123(9)109790s JOURNAL
Chimeric horse/human recombinant C9 proteins identify the amino acid sequence in horse C9 responsible for restriction of hemolysis
AUTHOR(S): Tomlinson, Stephen; Wang, Yunxia; Ueda, Etsuko; Esser, Alfred F.
LOCATION: Dep. Comparative Experimental Pathol., Univ. Florida Health Sci. Cent., Gainesville, FL, 32610, USA

JOURNAL: J. Immunol. DATE: 1995 VOLUME: 155 NUMBER: 1 PAGES: 436-44
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: chimeric horse human complement C9 hemolysis
DESCRIPTORS:
Antigens,CD59... Deoxyribonucleic acid sequences,complementary... Hemolysis ... Horse... Protein sequences...
chimeric horse/human recombinant C9 proteins identify amino acid sequence in horse C9 responsible for restriction of hemolysis in relation to CD59 interaction
CAS REGISTRY NUMBERS:
166025-65-6 amino acid sequence; chimeric horse/human recombinant C9 proteins identify amino acid sequence in horse C9 responsible for restriction of hemolysis in relation to CD59 interaction
80295-59-6 chimeric horse/human recombinant C9 proteins identify amino acid sequence in horse C9 responsible for restriction of hemolysis in relation to CD59 interaction
162159-77-5 nucleotide sequence; chimeric horse/human recombinant C9 proteins identify amino acid sequence in horse C9 responsible for restriction of hemolysis in relation to CD59 interaction

2/7/6
DIALOG(R)File 399:CA SEARCH(R)

122211724 CA: 122(17)211724q JOURNAL
Chimeras of human complement C9 reveal the site recognized by complement regulatory protein CD59
AUTHOR(S): Huesler, Thomas; Lockert, Dara H.; Kaufman, Kenneth M.; Sodetz, James M.; Sims, Peter J.
LOCATION: Blood Res. Inst., Blood Cent. Southeast. Wisconsin, Milwaukee, WI, 53201-2178, USA
JOURNAL: J. Biol. Chem. DATE: 1995 VOLUME: 270 NUMBER: 8 PAGES: 3483-6 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: complement C9 recognition sequence protein CD59, sequence complement C9 rabbit
DESCRIPTORS:
Antigens,CD59... Deoxyribonucleic acid sequences,complementary... Gene,animal... Protein sequences... Rabbit...
chimeras of human complement C9 reveal site recognized by complement regulatory protein CD59
CAS REGISTRY NUMBERS:
161631-71-6 amino acid sequence; chimeras of human complement C9 reveal site recognized by complement regulatory protein CD59
80295-59-6 chimeras of human complement C9 reveal site recognized by complement regulatory protein CD59
161657-70-1 nucleotide sequence; chimeras of human complement C9 reveal site recognized by complement regulatory protein CD59

2/7/7
DIALOG(R)File 399:CA SEARCH(R)

121228383 CA: 121(19)228383e JOURNAL
Identity of a peptide domain of human C9 that is recognized by the cell-surface complement inhibitor, CD59
AUTHOR(S): Chang, Chi-Pei; Huesler, Thomas; Zhao, Ji; Wiedmer, Therese; Sims, Peter J.

LOCATION: Blood Research Institute, Blood Center of Southeastern Wisconsin, Milwaukee, WI, 53233, USA
JOURNAL: J. Biol. [redacted]. DATE: 1994 VOLUME: 269 [redacted]ER: 42 PAGES: 26424-30 CODEN: JBC[redacted] ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement C9 CD59 binding region
DESCRIPTORS:
Molecular structure-biological activity relationship...
CD59-binding; of complement C9
Antigens,CD59... Peptides,biological studies...
identity of a peptide domain of human C9 that is recognized by CD59
CAS REGISTRY NUMBERS:
80295-59-6 identity of a peptide domain of human C9 that is recognized by CD59

2/7/8
DIALOG(R)File 399:CA SEARCH(R)

121171701 CA: 121(15)171701a JOURNAL
Antisense sequences of 20-kDa homologous restriction factor (HRF20) are found in C9 and the C8 .beta. chain of homologous complement
AUTHOR(S): Campbell, William; Baranyi, Lajos; Okada, Noriko; Okada, Hidechika
LOCATION: Sch. Med., Nagoya City Univ., Nagoya, Japan, 467
JOURNAL: Antisense Res. Dev. DATE: 1993 VOLUME: 3 NUMBER: 3 PAGES: 291-4 CODEN: AREDEI ISSN: 1050-5261 LANGUAGE: English
SECTION:
CA203003 Biochemical Genetics
CA213XXX Mammalian Biochemistry
CA215XXX Immunochemistry
IDENTIFIERS: antisense sequence HRF20 restriction factor complement
DESCRIPTORS:
Antigens,CD59...
antisense sequences of 20-kDa homologous restriction factor (HRF20) are found in C9 and the C8 .beta. chain of homologous complement
CAS REGISTRY NUMBERS:
80295-58-5 80295-59-6 antisense sequences of 20-kDa homologous restriction factor (HRF20) are found in C9 and the C8 .beta. chain of homologous complement

2/7/9
DIALOG(R)File 399:CA SEARCH(R)

120242128 CA: 120(19)242128m JOURNAL
A synthetic peptide from complement protein C9 binds to CD59 and enhances lysis of human erythrocytes by C5b-9
AUTHOR(S): Tomlinson, Stephen; Whitlow, Michael B.; Nussenzweig, Victor
LOCATION: Med. Cent., New York Univ., New York, NY, 10016, USA
JOURNAL: J. Immunol. DATE: 1994 VOLUME: 152 NUMBER: 4 PAGES: 1927-34
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement C9 cytolysis CD59 antigen
DESCRIPTORS:
Antigens,CD59...
complement C9 hinge region binding site for human, membrane attack complex-mediated cytolysis in relation to
Molecular structure-biological activity relationship...
complement C9-inhibiting, of CD59 antigen of humans
Cytolysis...

membrane attack complex-mediated, human CD59 antigen regulation of, binding site on complement C9 in
Molecular associatio[redacted]
of complement C9[redacted]th human CD59, C9 hinge region binding site in
CAS REGISTRY NUMBERS:
82986-89-8 CD59 binding site for human complement C9 in relation to cytolysis by
80295-59-6 hinge region domain of human, as CD59 binding site
154331-57-4 of complement C9 hinge region, in human CD59 regulation of membrane attack complex-mediated cytolysis

2/7/10
DIALOG(R)File 399:CA SEARCH(R)

120132221 CA: 120(11)132221d JOURNAL
Immunohistochemical determination of complement activation in joint tissues of patients with rheumatoid arthritis and osteoarthritis using neoantigen-specific monoclonal antibodies
AUTHOR(S): Kemp, Philip A.; Spragg, Julia H.; Brown, Judith C.; Morgan, B. Paul; Gunn, Catherine A.; Taylor, Peter W.
LOCATION: Res. Preclin. Dev., CIBA-Geigy Pharm., Horsham/West Sussex, UK, RH12 4AB
JOURNAL: J. Clin. Lab. Immunol. DATE: 1992 VOLUME: 37 NUMBER: 4
PAGES: 147-62 CODEN: JLIMDJ ISSN: 0141-2760 LANGUAGE: English
SECTION:
CA215008 Immunochemistry
IDENTIFIERS: complement activation synovium rheumatoid arthritis osteoarthritis
DESCRIPTORS:
Complement...
activation of, in synovial tissues from humans in osteoarthritis and rheumatoid arthritis
Arthritis,osteo-... Arthritis,rheumatoid...
complement activation in humans in
Synovial membrane...
complement components deposition in, from humans in osteoarthritis and rheumatoid arthritis
Blood vessel,endothelium,composition...
complement components on, in humans in osteoarthritis and rheumatoid arthritis
Antigens,CD59...
in synovial vessels from humans in osteoarthritis and rheumatoid arthritis
Antibodies,monoclonal...
to complement C3 and C9 epitopes, prepn. and reactivity of, with synovial tissues from humans in osteoarthritis and rheumatoid arthritis
CAS REGISTRY NUMBERS:
82986-89-8 in synovial tissue from humans in osteoarthritis and rheumatoid arthritis
80295-41-6P 80295-59-6P monoclonal antibodies to, prepn. and reactivity of, with synovial tissues from humans in osteoarthritis and rheumatoid arthritis

2/7/11
DIALOG(R)File 399:CA SEARCH(R)

120006497 CA: 120(1)6497k JOURNAL
Interactions of soluble CD59 with the terminal complement complexes. CD59 and C9 compete for a nascent epitope on C8
AUTHOR(S): Lehto, Timo; Meri, Seppo
LOCATION: Dep. Bacteriol. Immunol., Univ. Helsinki, Helsinki, Finland

JOURNAL: J. Immunol. DATE: 1993 VOLUME: 151 PAGES: 4941-9 CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: CD59 antigen complement C8 C9
DESCRIPTORS:
Antigens,CD59...
complement terminal components interaction with
Complement...
terminal components of, interaction of, with CD59 antigen
CAS REGISTRY NUMBERS:
80295-58-5 80295-59-6 83380-81-8 120860-66-4 CD59 antigen interaction with

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2/7/12
DIALOG(R)File 399:CA SEARCH(R)

117088287 CA: 117(9)88287s JOURNAL
The human complement regulatory protein CD59 binds to the .alpha.-chain of C8 and to the "b" domain of C9
AUTHOR(S): Ninomiya, Haruhiko; Sims, Peter J.
LOCATION: Oklahoma Med. Res. Found., Oklahoma City, OK, 73104, USA
JOURNAL: J. Biol. Chem. DATE: 1992 VOLUME: 267 NUMBER: 19 PAGES: 13675-80 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: CD59 binding domain complement C 8, antigen CD59 assocn complement C 9
DESCRIPTORS:
Antigens,CD59...
binding to complement C8 .alpha.-chain and complement C9b by, of humans
Molecular association...
of CD59 antigen with human complement C8 .alpha.-chain or C9b
CAS REGISTRY NUMBERS:
80295-58-5 CD59 antigen binding to .alpha.-chain of human
80295-59-6 CD59 antigen binding to b domain of human
83534-36-5 CD59 antigen binding to human

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DIALOG(R)File 399:CA SEARCH(R)

115133684 CA: 115(13)133684r JOURNAL
Inhibition of homologous complement by CD59 is mediated by a species-selective recognition conferred through binding to C8 within C5b-8 or C9 within C5b-9
AUTHOR(S): Rollins, Scott A.; Zhao, Ji; Ninomiya, Haruhiko; Sims, Peter J.
LOCATION: Cardiovasc. Biol. Res. Program, Oklahoma Med. Res. Found., Oklahoma City, OK, 73104, USA
JOURNAL: J. Immunol. DATE: 1991 VOLUME: 146 NUMBER: 7 PAGES: 2345-51
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: CD59 antigen homologous complement inhibition, C9 CD59 antigen homologous complement inhibition
DESCRIPTORS:
Hemolysis...
complement-mediated, CD59 antigen inhibition of homologous, species selectivity of, binding to complement C8 and C9 in
Antigens,CD59...
homologous complement inhibition by, species selectivity of, binding to

complement C8 and C9 in
Complement...
inhibition of ho[redacted]ogous, by CD59 antigen, speci electivity of,
binding to compl[redacted]nt C8 and C9 in
CAS REGISTRY NUMBERS:
82986-89-8 CD59 antigen binding to complement C8 and C9 of, in species-selective homologous complement inhibition
80295-58-5 80295-59-6 CD59 antigen binding to, of C5b-9 complex, in species-selective homologous complement inhibition

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DIALOG(R)File 399:CA SEARCH(R)

113189407 CA: 113(21)189407d JOURNAL
Human protectin (CD59), an 18,000-20,000 MW complement lysis restricting factor, inhibits C5b-8 catalyzed insertion of C9 into lipid bilayers
AUTHOR(S): Meri, S.; Morgan, B. P.; Davies, A.; Daniels, R. H.; Olavesen, M. G.; Waldmann, H.; Lachmann, P. J.
LOCATION: Mol. Immunopathol. Unit, Med. Res. Counc., Cambridge, UK, CB2 2QH
JOURNAL: Immunology DATE: 1990 VOLUME: 71 NUMBER: 1 PAGES: 1-9
CODEN: IMMUAM ISSN: 0019-2805 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: protectin complement cytolysis C9
DESCRIPTORS:
Cytolysis...
by complement, protectin inhibition of, C9 insertion into cell membrane inhibition in, of humans
Cell membrane...
complement C9 insertion into, C5b-8-catalyzed, human protectin inhibition of
Antigens,CD59... Sialoglycoproteins,protectins...
complement-mediated cytolysis inhibition by human, C9 insertion into cell membranes inhibition in
Complement...
cytolysis by, protectin inhibition of, C9 insertion into cell membranes inhibition in, of humans
CAS REGISTRY NUMBERS:
82903-91-1 complement C9 insertion into cell membranes catalyzed by, human protectin inhibition of
80295-59-6 insertion of, into cell membranes, C5b-8-catalyzed, human protectin inhibition of

2/7/15
DIALOG(R)File 399:CA SEARCH(R)

113057087 CA: 113(7)57087q JOURNAL
The complement-inhibitory activity of CD59 resides in its capacity to block incorporation of C9 into membrane C5b-9
AUTHOR(S): Rollins, Scott A.; Sims, Peter J.
LOCATION: Health Sci. Cent., Oklahoma Univ., Oklahoma City, OK, 73104, USA
JOURNAL: J. Immunol. DATE: 1990 VOLUME: 144 NUMBER: 9 PAGES: 3478-83
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement C9 inhibition CD59 antigen
DESCRIPTORS:
Complement...
activation of, CD59 antigen inhibition of, mechanism of human

Glycophospholipids,phosphatidylinositol-contg....
as membrane anchor for CD59 antigen
Marchiafava-Micheli [redacted]drome...
CD59 antigen exp[redacted]sion on erythrocytes of humans with
Cell membrane...
CD59 antigen of erythrocyte, complement-mediated lysis inhibition by, mechanism of human
Antigens,CD59...
complement inhibition by, mechanism of human
Hemolysis...
complement-mediated, CD59 antigen inhibition of, mechanism of human
CAS REGISTRY NUMBERS:
82903-91-1 assembly of, antigen CD59 inhibition of complement C9 incorporation in, of human
80295-58-5 binding of, to membrane-bound C5b-67, CD59 antigen effect on, of human
101754-00-1 complement C8 binding to membrane bound, CD59 antigen effect on, of human
82986-89-8 complement C9 incorporation into membrane-assocd., antigen CD59 inhibition of human
80295-59-6 polymn. of and incorporation into membrane complex C5b-9 of, antigen CD59 inhibition of, of human